Support for added Claim 25 is found in the specification in the paragraph bridging pages 22-23; page 23, lines 4-7; Example 36, pages 229-230; and Example 42, pages 247-248.

Added Claim 26 is supported in the specification by the paragraph bridging pages 22-23; page 23, lines 4-7, paragraph bridging pages 178-179; page 181, lines 10-28; pages 182-183; page 184, liens 1-17; paragraph bridging pages 211-212; page 212, lines 3-23.

New Claim 27 finds support in the specification at page 244, lines 17-24.

Support for new Claim 28 is found in the specification at page 207, lines 13-18 and the paragraph bridging pages 210-211.

Applicant's amendments do not introduce new matter.

2. Restriction Requirement

The Examiner required restriction between the following groups of inventions:

Group I: Claims 1-9

Group II: Claims 10-14; and

Group III: Claims 15-24.

In a telephone conversation with the Examiner Applicant provisionally elected, and hereby affirms its election without traverse, of Group II (*i.e.*, Claims 10-14).

3. Rejection of Claims 10-12 Under 35 U.S.C. § 112, First Paragraph

The Examiner rejected Claims 10-12 for lack of enablement on the grounds of (a) "the lack of guidance in the specification and the breadth of the claims", and (b) "lack of predictability of the art to which the invention pertains."[2]

Neither of the Examiner's statement meets the burden of establishing a *prima facie* case of non-enablement. It is established law that:

> "it is incumbent upon the Patent Office, whenever a rejection on [the basis of lack of enablement] is made, to *explain why* it doubts the truth or accuracy of any statement in a supporting disclosure *and* to back up assertions of its own

[2] Paper No. 5, item 9, page 5.

with *acceptable evidence or reasoning* which is inconsistent with the contested statement."[3]

Applicant urges that neither evidence nor reasoning advanced by the Examiner establishes a *prima facie* case of non-enablement.

A. The Examiner's Explanation Is Scientifically Unsound, And The Specification Provides Ample Guidance to One Skilled in The Art On How To Test The Biological Activity Of The Claimed Vaccines

The thrust of the Examiner's argument is that the skilled artisan cannot determine how to select the exact "portion" of the claims' recited sequences because such selection requires "a detailed knowledge of the ways in which the protein's structure relates to its function."[4] This statement is scientifically incorrect. Contrary to the Examiner's assertion, knowledge of the structure of a protein is **not necessary** to make or use a vaccine directed to that protein. Indeed, the specification discloses that a trivalent antitoxin for toxin types A, B, and E (*i.e.*, the toxins recited in the rejected claims) was commercially available in 1984,[5] prior to the cloning and sequencing of toxin types A,[6] B,[7] and E.[8] In other words, an antitoxin against these three proteins was **made** and **used** more than eleven years prior to the determination of the amino acid sequence, much less the **structure**, of these proteins.

The Examiner is reminded that the claimed invention relates to vaccines. Enablement under 35 U.S.C. §112, first paragraph is satisfied if the specification enables one of skill in

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[3] (Emphasis added) *In re Marzocchi*, 169 USPQ 367, 370 (CCPA 1971).

[4] Paper No. 5, item 9, page 4.

[5] Specification, page 7, lines ??

[6] The specification discloses that The *C. botulinum* type A neurotoxin gene was cloned and sequenced in 1990 (Specification, page 169, lines 23-24).

[7] The specification discloses that The *C. botulinum* type B neurotoxin gene was cloned and sequenced in 1992 and 1994 (Specification, page 227, lines 4-6).

[8] The specification discloses that The *C. botulinum* type E neurotoxin gene was cloned and sequenced from several different strains between the years 1990-1993 (Specification, page 244, lines 4-9).

the art to make and use the claimed vaccines. In this regard, the specification provides extensive guidance on how to test the biological activity of any portion of a *Clostridium botulinum* toxin as a vaccine.

General guidance is presented by the specification's teaching that monovalent and multivalent vaccines refer to compositions "which are capable of provoking an immune response in a host animal" directed against, respectively, a single and several types of clostridial toxin.[9] The specification further elaborates by pointing out that provoking an immune response means "[inducing] the production of antibodies which protect the host against challenge" with the toxin.[10]

Specific guidance is also taught with respect of determining the biological activity of any portion of the *Clostridium botulinum* toxins recited in Claims 10 and 11. As to *Clostridium botulinum* type A toxin, the specification teaches that an immune response to this toxin may be characterized using a mouse neutralization assay. The Examiner's attention is directed to the express teaching by the specification that:

> "[t]he mouse model is the art accepted method for . . . evaluation of anti-botulinal antibodies."[11]

In other words, the art recognizes this method as suitable for determining the **biological activity** of any immunogen (including any "portion" of a *Clostridium botulinum* toxin) as a vaccine. Specifically, the specification teaches that toxin A protein is mixed with adjuvant, injected subcutaneously in mice, the mice are subcutaneously boosted, and anti-*C. botulinum* serotype A toxoid titers determined using ELISA.[12] The ability of the anti-*C. botulinum* serotype A serum antibodies to neutralize native *Clostridium botulinum* type A toxin is then tested in the mouse neutralization assay as detailed in Examples 29 and 23b.[13] The LD_{50} of

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[9] Specification, paragraph bridging pages 22-23.

[10] Specification, page 23, lines 4-7.

[11] Specification, page 181, lines 15-19.

[12] Specification, paragraph bridging pages 211-212; page 212, lines 3-5.

[13] Specification, page 212, lines 9-23.

the serum is determined in mice,[14] and the serum
is used to immunize rats by nasal or oral administration, followed by a boost and collection of rat serum after 7 days.[15] Serum from boosted rats (or preimmune control serum) is mixed with several dilutions of the toxin A, the mixture is injected into mice, and the mice are observed for signs of botulism in order to determine if the serum neutralizes the effects of a challenge dose of toxin A (*e.g.*, prevents death of the mouse challenged with a lethal dose of the toxin).[16] This is followed by quantitation of neutralizing anti-toxin antibodies in the rat serum using methods known in the art.[17]

The specification also teaches that the art-accepted mouse neutralization assay is successfully used to determine the biological activity of portions of both the *Clostridium botulinum* type B toxin[18] and type E toxin[19] which are recited in rejected Claim 10.

In sum, because the Examiner's explanation and reasoning underlying the doubted enablement are scientifically erroneous, and in view of the detailed teaching of the specification on how biological activity of a vaccine can be determined using an art-accepted model, a *prima facie* case of non-enablement is not established.

B. Rudinger Does Not Foretell Unpredictability In the Relevant Art

In support of the argument that biological activity of a protein as a vaccine requires knowledge of the protein's structure, the Examiner provided as evidence a reference by Rudinger. The Examiner argued that Rudinger succinctly expresses "the true fact of the state of the art in peptide chemistry" when it states that "the significance of particular amino acids

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[14] Specification, page 181, lines 27-28; page 182, lines 1-21.

[15] Specification, paragraph bridging pages 178-179.

[16] Specification, paragraph bridging pages 182 and 183.

[17] Specification, page 183, lines 4-23; page 184, lines 1-17.

[18] Specification, Example 36, pages 229-230.

[19] Specification, Example 42, pages 247-248.

and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study."[20]

The evidentiary value of Rudinger is, at best, minimal for two reasons. First, Rudinger was published in 1976, *i.e.*, a full **21 years** prior to the filing date of the instant application. This extensive lapse of time between the publication date of Rudinger and the filing date of the claimed invention make dubious Rudinger's teachings in so far as they apply to the claimed vaccines.

Second, the value (if any) of Rudinger's teachings is further diminished since it pertains to a different field from that of the claimed vaccines. Rudinger relates not to vaccines, but to the ability of hormones to bind to receptors. Rudinger essentially argues that while the ability of a protein to bind a receptor molecule cannot be determined from the amino acid sequence of the protein, such ability may be functionally (rather than structurally) determined. Nothing in Rudinger speaks to the biological activity of vaccines recited in the rejected claims.

Since Rudinger falls short of providing "acceptable evidence," and since the Examiner's reasoning is scientifically unsound, a *prima facie* case of non-enablement is lacking. Accordingly, the rejection of Claims 10-12 is in error and should be withdrawn.

4. Rejection of Claims 10-14 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected Claims 10-14 under 35 U.S.C. § 112, second paragraph for alleged indefiniteness on two grounds. First, the Examiner argued that the term "portion of" in Claims 10-12 is indefinite "because the relevant portions have not been identified."[21] The Examiner is respectfully reminded that:

> "Claims of a patent application '*are to be construed in the light of the specification* and the understanding thereof by those skilled in that art to whom they are addressed'."[22]

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[20] Paper No. 5, item 9, page 4.

[21] Paper No. 5, item 10, page 5.

[22] *Application of Salem*, 553 F.2d 676, 683, 193 USPQ 513 (CCPA 1977) (quoting *In re Myers*, 410 F.2d 420, 425 (CCPA 1969) with emphasis added in *Salem*).

It is not the function of the claims to identify the relevant portions of the toxins, so long as identification of such portions is understood by the artisan from the specification's teachings. The specification leaves no doubt as to the intended meaning of the term "portion" when it teaches that:

> "As used herein the term 'portion' when in reference to a protein (as in 'a portion of a given protein') refers to fragments of that protein. The fragments may range in size from four amino acid residues to the entire amino acid sequence minus one amino acid."[23]

As the term "portion of" is succinctly defined in the specification, a rejection based on indefiniteness cannot stand.

Second, the Examiner argued that Claims 10-11 are indefinite for reciting "at least a portion of" because it is unclear how much of the *Clostridium* peptide is required.[24] The artisan need go no farther than the specification to construe this term. The immediately preceding quotation from the specification explains what a "portion" of a toxin is, *i.e.*, a fragment ranging in size from 4 amino acids to the entire amino acid sequence minus one amino acid. Common sense dictates that the objected-to term "*at least* a portion of" means a fragment which includes both (a) fragments which constitute a "portion" as described above, and (b) fragments which are **larger** in size than a "portion." In other words, the term "at least a portion of" a toxin means fragments which range in size from 4 amino acids to the entire amino acid sequence of the toxin. Since definiteness is not defeated by the artisan's use of common sense, this rejection is erroneous and should be withdrawn.

5. Rejection of Claims 10-14 Under 35 U.S.C. § 103

Claims 10-14 stand rejected for obviousness under 35 U.S.C. § 103 based on Thompson *et al.* in view of Binz *et al.*, Roitt, LeClerc *et al.*, Kleid, and Siegel. Applicant respectfully traverses.

The Court of Appeals of the Federal Circuit has held that:

> "[T]he examiner bears the initial burden, on review of the prior art or on any other ground, of presenting a *prima facie* case of unpatentability. . . . If examination at the initial stage does not produce a *prima facie* case of

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[23] Specification, page 19, lines 3-6.

[24] Paper No. 5, item 10, page 5.

> unpatentability, then without more the applicant is entitled to grant of the patent."[25]

Applicant asserts that the Examiner has not met the burden of establishing a *prima facie* case of obviousness.

A *prima facie* case of obviousness requires the Examiner to cite to a combination of references which (a) discloses the elements of the claimed invention, (b) suggests or motivates one of skill in the art to combine those elements to yield the claimed combination, and (c) provides a reasonable expectation of success should the claimed combination be carried out.[26] Failure to establish any **one** of these requirements is, without more, a failure to meet the Examiner's burden. Applicant urges that the Examiner has failed to establish, not one, but **all three** requirements, thus entitling Applicant to withdrawal of this rejection.

In addressing the obviousness rejection, Applicant's following arguments focus on independent Claim 10 since nonobviousness of an independent claim necessarily leads to nonobviousness of any claim depending therefrom.[27]

A. The Combined References Do Not Teach All The Elements of The Claimed Invention

It is axiomatic that the threshold requirement of a *prima facie* case of obviousness is that:

"all the claim limitations must be taught or suggested by the prior art."[28]

However, the cited references fail to meet this requirement. Independent Claim 10 recites the following elements: (a) a vaccine, (b) comprising a fusion protein, (c) where the fusion protein comprises (i) a non-toxin protein sequence, and (ii) at least a portion of *Clostridium*

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[25] *In re Oetiker*, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992).

[26] See, *e.g.*, *Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990); *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988).

[27] MPEP 2143.03, citing *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

[28] MPEP 2143.03, citing *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

botulinum type B toxin and/or type E toxin.[29] The Examiner conceded that the primary reference by Thompson *et al.* does not disclose **any** of Claim 10's elements by stating that:

> "Thompson et al. do not teach a vaccine comprising a fusion protein, said fusion protein comprising a non-toxin protein sequence and at least a portion of a *Clostridium botulinum* toxin, said toxin selected from the group consisting of type B toxin and type E toxin."[30]

The Examiner then continued to list what the secondary references purportedly teach. It is notable, however, that **none** of the cited references teaches elements (c)(i) or (c)(ii) since none of them discloses the complete amino acid sequence of *Clostridium botulinum* type B toxin and/or type E toxin.

Because the cited references do not satisfy the threshold requirement of *prima facie* obviousness, this rejection should be withdrawn.

B. There Is No Motivation To Combine The References' Teachings

The Examiner's sole reference to the "motivation" requirement is that "a person of ordinary skill in the art would have been motivated at the time of the invention to immunize with fusion proteins comprising portions of type A toxin, type B toxin, and type E toxin polypeptide of type A, substituting the fusion peptides for a step in the immunization series or boosts with the pentavalent botulinum (ABCDE) toxoid vaccine in order to increase the response to type A and type E botulinum toxin because the response to toxins A and E needed improvement."[31]

Prior to addressing the "motivation" requirement of a *prima facie* case of obviousness, Applicant first desires to correct an apparent misapprehension of the scope of the rejected claims. Independent Claim 10 does **not require** type A toxin because the language of Claim

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[29] The specification teaches that the claimed vaccine is not limited to monovalent vaccines but may be "a monovalent vaccine (*i.e.*, containing only a toxin B fusion protein or a toxin E fusion protein), a bivalent vaccine (*i.e.*, containing both a toxin B fusion protein and a toxin E fusion protein) or a trivalent or higher valency vaccine." Specification, page 26, lines 24-27.

[30] Paper No. 5, item 13, page 7.

[31] Paper No. 5, item 13, page 8.

10 expressly refers to only toxin types B and E, but not type A. Thus, any reference by the Examiner to *Clostridium botulinum* type A toxin is irrelevant to a discussion of obviousness of independent Claim 10 and of Claims 11-14 which depend therefrom.

In addressing the "motivation" requirement, Applicant respectfully reminds the Examiner that an argument in support of "motivation" requires an explanation which (a) is based on logic and is supported by sound scientific reasoning, **and** (c) supplies sufficient impetus to have led one of ordinary skill in the art to combine the teachings of the references to make the claimed invention.[32] As discussed below, these requirements are lacking in their entirety from the Examiner's single argument regarding motivation.

i. The Examiner's Statement Is Devoid Of Logic To Combine The Teachings of The References, And Fails To Provide Sound Scientific Reasoning In Support Of Substituting Fusion Peptides With A Pentavalent Peptide

As to the logic in support of combining the references, the law requires that:

> "[t]here must be some logical reason, apparent from positive concrete evidence of record, which justifies a combination of primary and secondary references"[33] and that "[t]he Examiner must indicate the reasons *why* one skilled in the art would have substituted an element of teaching of a first reference for that part of the second."[34]

However, the Examiner's statement is unclear as to what bearing (if any) the cited references (*i.e.*, the evidence of record) have in providing such logic. For example, the Examiner conceded that the primary Thompson *et al.* reference discloses only the amino acid sequence of **toxin A**.[35] As discussed above, the sequence of toxin A is irrelevant to a discussion of Claim 10's obviousness.

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[32] *Ex parte Levengood*, 28 USPQ2d 1300, 1301 (Pat. Bd. Appeals & Interf. 1993).

[33] *In re Regel*, 526 F.2d 1399 (CCPA 1975).

[34] *Ex parte Skinner*, 2 USPQ2d 1788, 1790 (Bd. Pat. App. & Int'f 1986).

[35] Paper No. 5, item 13, paragraph bridging pages 6-7, and first full paragraph of page 7.

Similarly, the Examiner's singular reference to Binz *et al.* is that this reference teaches "the complete sequence of type A and a partial sequence of Type E."[36] Again, Binz *et al.*'s teaching of the complete sequence of type A toxin is irrelevant, and a teaching of only a **partial** sequence of Type E toxin provides less than adequate "logic" to combine this reference with any other.

As to Roitt, the Examiner merely asserted that this reference "teaches that recombinant antigens can be generated such as viral epitopes and synthetic peptides."[37] How such disclosure logically relates to making vaccines in general, and to fusion proteins in particular is neither discussed nor alluded to by the Examiner. Indeed, Roitt does not discuss any of the elements of Claim 10 listed above. There cannot be "logic" in the Examiner's mere naming of a reference and stating what the reference purportedly teaches. An explanation of the nexus between the teachings of the various references is required.

The Examiner also refered to LeClerc *et al.* and to Kleid in support of the notion that "use of fusion proteins in vaccine production is well known in the art."[38] However, the existence of a method for making a composition is irrelevant to obviousness of the composition. The Federal Circuit has held that:

> "the existence of a general method of isolating [a composition] . . . is essentially irrelevant to the question whether the specific [composition] . . . would have been obvious, in the absence of other prior art that suggests the claimed [composition] . . . There must, however, still be prior art that suggests the claimed compound in order for a *prima facie* case of obviousness to be made out."[39]

Since Claim 10 is directed to a vaccine, not to a method of making or using a vaccine, the methods taught by LeClerc *et al.* and Kleid are irrelevant to obviousness of the vaccines of Claim 10 and of claims dependent therefrom.

With respect of Siegel, this reference discloses two pentavalent *Clostridium botulinum* toxoids both of which contain botulinum toxins of types A, B, C, D, and E adsorbed to

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[36] Paper No. 5, item 13, page 7.

[37] Paper No. 5, item 13, page 7.

[38] Paper No. 5, item 13, page 7.

[39] *In re Deuel*, 51 F.3d 1552, 34 USPQ2d 1210 (Fed. Cir. 1995).

aluminum phosphate. One of the two toxoid preparations was manufactured by Parke, Davis and Co. (PDC), while the other was produced by the Michigan Department of Public Health (MDPH).[40] Siegel discloses that while both toxoid preparations were made using the same methodology,[41] "the human response to two lots of the MDPH product was significantly greater than to the PDC product for the type B component, but the responses to types A and E did not differ."[42] The Examiner stated that the artisan would have been motivated to **substitute** the fusion proteins comprising portions of type A toxin, type B toxin, and type E toxin polypeptide with the pentavalent botulinum (ABCDE) toxoid vaccine in order to increase the response to type A and type E botulinum toxin because the response to toxins A and E needed improvement. This statement lacks logic in support of motivation to substitute the proteins of Siegel's vaccine with the fusion proteins recited in Claim 10 for four reasons.

First, as discussed above, substitution in so far as it pertain to toxin type A is **irrelevant** to a determination of obviousness of Claim 10.

Second, even if the artisan sought to improve the response to toxin E, the Examiner's statement does not explain **why** the artisan would be motivated to substitute the formalin-inactivated toxin E of Siegel with the claimed invention's fusion protein comprising toxin E.

Third, the Examiner's statement is conspicuously silent on **why** the skilled artisan would include in the vaccine a fusion protein comprising type B toxin to arrive at the claimed vaccine, particularly in view of Siegel's disclosure that the "human response to two lots of the MDPH product was *significantly greater* than to the PDC product for the type B component."[43]

Fourth, Kleid teaches away from any purported motivation (if such motivation were implausibly argued) to substitute Siegel's formalin-inactivated type B and type E toxins with the fusion proteins recited in Claim 10. The Examiner is respectfully reminded that:

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[40] Siegel, page 2351, columns 1 and 2.

[41] The toxoids are partially-purified and formalin-inactivated.

[42] Siegel, page 2351, column 2.

[43] (Emphasis added) Siegel, page 2351, column 2.

> "the prior art references relied upon must be considered in their entirety . . . disclosures in the references that diverge from and teach away from the invention cannot be disregarded."[44]

Kleid discloses the production of a recombinant fusion protein in which one of the structural proteins (VP_1) of the foot-and-mouth disease (FMD) virus is ligated to a peptide encoded by the *E. coli* tryptophan operon. The expressed fusion protein is purified and administered to cattle to protect against challenge contact with infected animals. Kleid teaches that fusion proteins produced by bacteria suffer from the problems that (a) "the immunogenic site may not be properly exposed," (b) "the peptide sequence(s) within that site may not be able to form into the correct configuration," and (c) the immunogenic site may require disulfide bonding to bring two distant parts of a protein or two different peptide chains into close proximity to form an antigenic site."[45] The Examiner did not examine these teachings of Kleid. Instead, the Examiner merely asserted that an artisan would have been motivated to immunize with fusion proteins. Failure to consider the factual content of the prior art is clear error.

For these additional four reasons, the Examiner's statement does not provide the necessary logic and reasoning required to show motivation to combine the teachings of the cited references.

ii. The Examiner's Explanation Lacks The Necessary Impetus To Combine The References

The second prong of the "motivation" requirement mandates that:

> "the examiner's explanation should be such that it provides that impetus necessary to cause one skilled in the art to combine the teachings of the references to make the proposed modification."[46]

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[44] *Dow Chemical Co. v. United States*, 20 Cl. Ct. 623, 630, 18 USPQ2d 1657, 1662 (Cl. Ct. 1990).

[45] Kleid, page 29, SUMMARY.

[46] *Ex parte Levengood*, 28 USPQ2d 1300 (Pat. Bd. Appeals & Interf. 1993), fn.2., citing *In re Albrecht*, 514 F.2d 1385, 185 USPQ 585 (CCPA 1975) and *Fromson v. Advance Offset Plate Inc.*, 720 F.2d 1565, 219 USPQ 1137 (Fed. Cir. 1983).

However, the Examiner's naked assertion does not provide the impetus necessary to motivate the art skilled to combine the references' teachings. The Examiner does nothing more than adhere to the approach of asserting conclusory statements in the absence of logic and reasoning. This falls far short of the standard of "compelling" motivation which the Board has found necessary to establish obviousness.[47]

In sum, there is no motivation to combine the references because the Examiner advances mere assertions rather than logic and sound scientific reasoning which provide an impetus to combine the references and to substitute their teachings to arrive at the claimed vaccines. Failure to establish this requirement is alone sufficient to negate a *prima facie* case of obviousness.

C. The Combined References Do Not Teach A Reasonable Expectation Of Success In Practicing The Claimed Invention

The Examiner also failed to establish that the references teach a reasonable expectation of success in producing the claimed vaccines. The Examiner's sole reference to the "expectation of success" requirement is found in the assertion that "[a] person of ordinary skill in the art would have had ample expectation of success of being able to utilize such methods because such methodology was well known in the art at the time the invention was made."[48] As discussed above, the Federal Circuit has flatly rejected the notion that mere availability of a method of making a claimed composition makes the composition obvious.[49] Thus, the Examiner's misplaced reliance on the availability of methods for making fusion proteins defeats establishment of this elements of a *prima facie* case of obviousness.

Moreover, the Examiner engages in the impermissible practice of failing to consider the teachings of the cited references in their entirety.[50] Kleid expressly teaches away from using fusion proteins as vaccines; Kleid states that although foot-and-mouth-disease virus VP_1-

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[47] *Ex parte Kranz*, 19 36 USPQ2d 1216 (Bd. Pat. App. & Int'f. 1990).

[48] Paper No. 5, item 13, page 8.

[49] *In re Deuel*, 51 F.3d 1552, 34 USPQ2d 1210 (Fed. Cir. 1995).

[50] *Dow Chemical Co. v. United States*, 20 Cl. Ct. 623, 630, 18 USPQ2d 1657, 1662 (Cl. Ct. 1990).

specific fusion proteins are effective vaccine, "[w]hether this method of vaccine production can be extended to many other immunogenic proteins from other organisms is not known."[51] Thus, Kleid teaches away from the element which requires a fusion protein as set forth in rejected Claim 10. At best, Kleid provides an invitation to experiment, and such an invitation is insufficient to sustain a rejection based on obviousness.

Moreover, the Examiner relied on hindsight guidance from the application at issue and this is not allowed as a basis for rejecting the claims.

> "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher."[52]

In sum, the claims were used as a frame, and individual, naked parts of separate prior art references were employed as a mosaic to recreate a facsimile of the claimed invention. At no point did the Examiner explain why that mosaic could have been obvious to one skilled in the art, or what there was in the prior art to disregard the teachings there found against making just such a mosaic. On the contrary, no reasoning or evidence was presented that one skilled in the art would have made vaccines containing fusion proteins in which a non-toxin protein is ligated to at least a portion of a *Clostridium botulinum* type B toxin and/or type E toxin, or would have been able to predict what would happen if they did.

Accordingly, Applicant submits that the Examiner has failed to meet the initial burden of presenting a *prima facie* case of obviousness. The rejection of Claims 10-12 under §103 is thus in error and should be withdrawn.

6. Rejection of Claims 13 And 14 Under 35 U.S.C. § 103

Claims 13 and 14 were further rejected for obviousness under 35 U.S.C. § 103 based on Thompson *et al.*, in view of Binz *et al.*, Roitt, LeClerc *et al.*, Kleid, and Siegel and further in view of Ford *et al.* Applicant cannot agree because a *prima facie* case of obviousness is not established.

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[51] Kleid, page 29, SUMMARY.

[52] *W.L. Gore & Assoc. v. Garlock, Inc.*, 721 F.2d 1540, 1550, 220 USPQ 303, 311 (Fed. Cir. 1983).

A. The Combined References Do Not Disclose All The Elements Of Claims 13 and 14

As discussed above, the threshold requirement in a *prima facie* case of obviousness is the provision of references which disclose all the limitations of the claimed invention.

As to both Claims 13 and 14, Applicant reiterates the impropriety of the Examiner's combination of Thompson *et al.*, Binz *et al.*, Roitt, LeClerc *et al.*, Kleid, and Siegel since **none** of the references discloses the complete amino acid sequence of *Clostridium botulinum* type B toxin and/or type E toxin. Ford *et al.* does not remedy this deficiency because it also fails to provide this missing disclosure.

With regard to Claim 14, the cited combination of references suffers from the additional shortfall of failing to disclose the element of "substantially endotoxin-free" vaccines.

Since the cited references do not disclose **all** the elements of rejected Claims 13 and 14, a *prima facie* case of obviousness is defective.

B. There Is No Motivation To Combine The References To Make Vaccines Which Contain Fusion Proteins Comprising a Poly-Histidine Tract, Or To Make Substantially Endotoxin-Free Vaccines

As discussed above, the Examiner bears the burden of providing an explanation based on logic and sound scientific reasoning, as well as providing sufficient impetus to lead one of ordinary skill in the art to combine the teachings of the references to make the claimed vaccines.[53] This burden has not been met with respect to either Claim 13 or 14.

As to Claim 13, the Examiner advanced two arguments in support of motivation. The first argument was that "a person of ordinary skill in the art would have been motivated at the time of the invention to generate fusion proteins consisting of toxin A, toxin B or toxin E, or combination of the individual toxins together with a non-toxin protein sequence such as poly(his) [for] *purification* and *recovery* of the recombinant toxins."[54] This argument does not provide the necessary motivation for three reasons.

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[53] *Ex parte Levengood*, 28 USPQ2d 1300, 1301 (Pat. Bd. Appeals & Interf. 1993).

[54] (Emphasis added) Paper No. 5, item 14, page 9.

First, Claim 13 depends from Claim 10 and neither claim recites fusion proteins containing toxin A. Therefore, any reference to toxin A is **irrelevant** to an obviousness analysis of Claim 13.

Second, Applicant incorporates by reference the above-discussed arguments with respect to the obviousness rejection of Claims 10-14. In short, the Examiner has not provided either logic or sound scientific reasoning to provide an impetus to combine the teachings of Thompson *et al.*, Binz *et al.*, Roitt, LeClerc *et al.*, Kleid, and Siegel, thus failing to provide motivation to combine these references.

Third, the Examiner's further citation of Ford *et al.* does not overcome the deficient motivation to make the claimed invention. Claim 13 is directed to a "vaccine," not to a "recovered" or "purified" protein. This distinction is significant because, whereas a claimed vaccine (as defined in the instant application) against a *Clostridium botulinum* toxin must be capable of **inducing antibodies** in an immunized host which are capable of **protecting against a challenge** with that toxin, the "recovered" or "purified" proteins of Ford *et al.* do not exhibit such properties. Specifically, the specification teaches that a monovalent *C. botulinum* type A toxin vaccine "*induces antibodies* in the immunized host which *protect* against a challenge with type A toxin" while a multivalent *C. botulinum* type A toxin and type B toxin vaccine "*induces the production of antibodies* which *protect* the host against a challenge with both type A and B toxin."[55] In contrast, Ford *et al.* relates only to the use of fusion proteins for the **recovery** and **purification** of proteins, and not to the generation of proteins which induce antibodies and which are capable of protecting against challenge with a toxin. Thus, one of skill in the art may arguably be motivated by Ford *et al.* to use fusion proteins to recover and purify a protein, but not to make a vaccine which induces antibodies that are protective against *C. botulinum* toxin challenge. For the reasons discussed above, the Examiner's first argument fails to provide the requisite motivation to combine the references to arrive at the invention of Claim 13.

The Examiner's second argument is that "[f]ollowing LeClerc's example of using fusion proteins for vaccination, one would have been motivated to substitute poly-histidine for

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[55] (Emphasis added) Specification, paragraph bridging pages 22-23.

the maltose binding proteins of LeClerc *et al* in order to facilitate purification of the fusion protein and thus ensure large quantities of pure immunogen."[56]

A first problem with this argument is that it does not explain **why** one would replace the maltose binding protein (MBP) of LeClerc's fusion protein with the poly-histidine of Claim 13's fusion protein.

A second problem with the Examiner's argument is that it erroneously presupposes that the biological activity of one fusion protein predicates biological activity of another fusion protein in which **each** of the protein constituents is **different**. No sound scientific reasoning has been advanced in support of such an assumption.

Referring to Claim 14, the Examiner argued that "[i]t would have been obvious for one to keep the vaccine endotoxin-free as that was the standard of the art for a pharmaceutical at the time the invention was made."[57] While it may have been desirable to make substantially endotoxin-free vaccines, the Federal Circuit has clearly stated that:

"A general incentive does not make obvious a particular result . . ."[58]

Thus, the existence of a standard in the art does not make the substantially endotoxin-free vaccines of Claim 14 obvious.

Based on the above, the Examiner has failed to establish the requisite motivation to combine the cited references for the purpose of making the vaccines of Claim 13 or 14, thus necessitating withdrawal of the rejection under §103.

C. There Is No Expectation Of Success In Making Vaccines Which Contain Fusion Proteins Comprising a Poly-Histidine Tract, Or Making Substantially Endotoxin-Free Vaccines

The burden is squarely placed on the Examiner to establish an expectation of success in practicing the claimed invention. The Examiner attempted to meet this burden by stating that "[a] person of ordinary skill in the art would have had ample expectation of success of being able to utilize the above methods because such methodology was well known in the art

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[56] Paper No. 5, item 14, page 9.

[57] Paper No. 5, item 14, page 9.

[58] *In re Deuel*, 51 F.3d 1552, 34 USPQ2d 1210 (Fed. Cir. 1995).

at the time the invention was made."[59] However, as explained above, availability of a method of making a claimed composition does not make the composition obvious.[60] Therefore, as to both rejected Claims 13 and 14, the Examiner's attempt must fail.

Additionally, with respect of Claim 13, Ford *et al.* teaches away from producing biologically active vaccines through the use of fusion protein technology. Ford *et al.* discloses that **insolubility** of expressed fusion proteins is a common problem in expressing foreign proteins. The authors state that:

> "Many foreign proteins expressed intracellularly at high levels in *E. coli* and yeasts are produced as insoluble aggregates, often called refractile or inclusion bodies . . . Inclusion body formation is not limited to intracellular expression but can take place in the *E. coli* periplasm as well."[61]

The authors also warn that solubilization requires complete **denaturation** followed by refolding. They state that:

> "In inclusion bodies, proteins exist in a partially unfolded state and usually cannot be solubilized without the use of strong chaotropic agents such as guanidine hydrochloride or urea. After this treatment, the proteins are completely denatured and must be refolded during or after removal of the denaturing agent."[62]

The specification warns that "[t]he harsh treatment of inclusion body protein needed to accomplish this solubilization may reduce the immunogenicity of the purified protein."[63] This concern over the **biological activity** of the expressed fusion protein was echoed by Ford *et al.* which states that one of the considerations for using a fusion system for expression is whether the fusion partner will "interfere with *biological activity* of the target."[64] Thus, Ford *et al.* teaches away from making the claimed biologically active vaccines through the use of fusion

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[59] Paper No. 5, item 14, page 9.

[60] *In re Deuel*, 51 F.3d 1552, 34 USPQ2d 1210 (Fed. Cir. 1995).

[61] Ford *et al.*, paragraph bridging pages 101 and 102.

[62] Ford *et al.*, paragraph bridging pages 101 and 102.

[63] Page 43, sentence beginning on line 27.

[64] (Emphasis added) Ford *et al.*, page 101, column 1.

protein technology since it discloses that expression of a protein as a fusion protein may negatively impact the protein's biological activity, which is a requisite for a useful vaccine.

In view of the above, Applicant submits that the Examiner did not meet the burden of proof in establishing a *prima facie* case of obviousness. Accordingly, the rejection of Claims 13 and 14 under 35 U.S.C. §103 should be withdrawn.

7. Conclusion

All grounds of rejection and objection of the Office Action of May 28, 1997 having been addressed, reconsideration of the application is respectfully requested. It is respectfully submitted that the invention as claimed fully meets all requirements and that the claims are worthy of allowance.

Dated: November 24, 1997

Virginia S. Medlen
Registration No. 32,050

Please direct all communications to:

Peter G. Carroll
Registration No. 32,837

MEDLEN & CARROLL, LLP
220 Montgomery Street, Suite 2200
San Francisco, California 94104
415/705-8410

APPENDIX I
PENDING CLAIMS

10. (Once Amended) A vaccine comprising a fusion protein, said fusion protein comprising a non-toxin protein sequence and at least a portion of [a] one or more *Clostridium botulinum* [toxin] toxins, said [toxin] one or more toxins selected from the group consisting of type B toxin and type E toxin.

11. The vaccine of Claim 10 further comprising a fusion protein comprising a non-toxin protein sequence and at least a portion of *Clostridium botulinum* type A toxin.

12. The vaccine of Claim 10, wherein said portion of said *Clostridium botulinum* toxin comprises the receptor binding domain.

13. The vaccine of Claim 10 wherein said non-toxin protein sequence comprises a poly-histidine tract.

14. The vaccine of Claim 10, wherein said vaccine is substantially endotoxin-free.

25. (New) The vaccine of Claim 10, wherein said vaccine is protective against a challenge with said one or more *Clostridium botulinum* toxins.

26. (New) The vaccine of Claim 11, wherein said vaccine is protective against a challenge with said *Clostridium botulinum* type A toxin.

27. (New) The vaccine of Claim 10, wherein said portion of *Clostridium botulinum* type B toxin is selected from the group consisting of SEQ ID NO:44 and SEQ ID NO:46, and said portion of *Clostridium botulinum* type E toxin is selected from the group consisting of SEQ ID NO:54 and SEQ ID NO:56.

28. (New) The vaccine of Claim 11, wherein said portion of *Clostridium botulinum* type A toxin is selected from the group consisting of SEQ ID NO:26 and SEQ ID NO:36.